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TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
DAVIS, MINH TAM B	
ART UNIT	**PAPER NUMBER**
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/016,737	MURPHY ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-37* is/are pending in the application.

4a) Of the above claim(s) *25, 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,24,26 and 28-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 23, 24, 26, and 28-37 are being examined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 23, 31-32, 33-37 remain rejected under 35 USC 103(a) as being obvious over Sallusto et al, 1994 (J Exp Med, 179: 1109-1118, of record), in view of Bigotti G et al, 1991 (Prostate, V19, N1, p.73-87), as evidenced by Inaba K et al, 1987 (Journal of experimental medicine (UNITED STATES), 166 (1) p:182-94, of record), for reasons already of record in paper of 10/16/07.

The response asserts as follows:

Bigotti et al do not teach a prostate antigen for any purpose. The Examiner has cited to the abstract and to page 85 of Bigotti et al. as supporting the conclusion that a prostate antigen is taught to replace the tetanus toxoid of Sallusto et al.. As noted in the prior response there is no teaching of a prostate antigen found in either the abstract or on page 85 of Bigotti et al. or anywhere else in the article. The statement in the abstract that comes closest to the Examiner's contention reads: "..., since LCs and HLA class II molecules may provide a means of eliciting the immune response, both LCs and,epithelial cells expressing Class II molecules being capable

of direct antigen presentation to immune cells." The Examiner infers that Bigotti et al. teach presentation of prostate antigen to the immune system. This interpretation of the language in Bigotti et al. is not correct and that the Examiner is using Applicants' disclosure to reconstruct the present invention. The teachings of Bigotti et al. cited by the Examiner, such as the correlation of LC and tumor grade, the expression of class II molecules by LCs and tumor cells, and the dependence of antigen presenting properties on class II expression, have no bearing on the pending claims, since these characteristics when either considered alone or in any combinations do not infer that human DC exposed in vitro to a prostate antigen can-uptake and present the prostate, antigen and activate T cells specific to the prostate antigen, which is the subject matter of the present claims.

In fact, a careful reading of Bigotti et al. would lead to different conclusions than those set forth by the Examiner. In particular, if in fact the LCs present in the low grade carcinomas were to present prostate antigen to the immune system, one skilled in the art would expect infiltration of immune cells to those locations. Indeed, Bigotti et al. examine their histological samples for such infiltrates. (See page 77 bridging to pages 78 and 79). Bigotti et al. state "[f]inally we examined all the sections for lymphoid infiltrate, but we found that lymphocytes were scarce in all the tumors, regardless of the degree of differentiation, and were mostly present at the peripheral border of the tumor as small aggregates," "Instead we found that low-grade carcinomas were very rich in HLA-class II-positive, interstitial, oval to elongated cells, which were sometimes in close contact with tumor glands (Fig 12), mostly representing macrophages and in only small percentages LCs, as comparing the adjacent S-100- stained section." These results are reviewed in the discussion section found on pages 82-85 of Bigotti et al, where the

authors state "[l]astly, we did not find a correlation among cytological grade, HLA-class II expression, LCs, and lymphoid infiltrate as the latter was present mostly at the periphery of tumors as aggregates and did not show close contact with the malignant glands; instead we found a correlation among the aforementioned parameters and the presence of interstitial oval to elongated HI, A class II positive cells,-interpretable as macrophages, histiocytes, and activated fibroblasts; comparison with the corresponding S-100-stained section showed only a minimal .part of these cells corresponded to LCs." The authors' final conclusion was that as there was evidence in the art to support that macrophage play an important roll in tumor rejection, the environment described by their results indicated that a similar mechanism was involved. Clearly, Bigotti et al. correlate tumor rejection and lymphocytic infiltrates with the presence of macrophage and not with the presence of LCs. Therefore, the reference would direct the skilled artisan away from combining the references as suggested by the Examiner and towards the use of macrophage to induce immune-mediated tumor rejection. In the present Office Action the Examiner has not provided any reasoning or teachings that address this issue.

The response has been considered but is not found to be persuasive for the following reasons:

Bigotti et al teach that both LCs and epithelial cells expressing MHC class II molecules are capable of direct antigen presentation to immune cells, and **LCs** and HLA class II molecule may provide a means of **eliciting the immune response** (abstract). Bigotti et al further teach that **LCs act as antigen presenting cells in this neoplastic** (i.e., prostate carcinoma) environment, while HLA class II molecules expressed by neoplastic epithelium interact primarily or **with the aid of LCs** with macrophages and secondarily with T helper lymphocytes **causing** expansion of

cytotoxic T cells and enhancement of the antibody response to membrane-bound **tumor associated antigens**, therefore providing a means for controlling the escape from the immune surveillance (Bigotti et al, p.85, item under Conclusions). Bigotti et al further teach that LCs function as antigen presenting cells, and these properties are dependent on Class II MHC expression, which provides T cell recognition elements for **antigen-specific** T helper-assisted **immune response**, such as expansion of cytotoxic T cell clones and enhancement of antibody response (Bigotti et al, p.74, 4th and 5th paragraph).

The antigen presented by LCs to immune cells, and subsequent elicitation of the immune response, as stated in the abstract of Bigotti et al, i.e., presentation of the antigen by LCs to T cells, is clearly **prostate cancer antigen**, because:

1) The immune response, i.e., cytotoxic T cells expansion and the antibody response, are **specific** to membrane-bound prostate **tumor associated antigens**, in view of the teaching in the abstract and on page 74, 85 in Bigotti et al, and

2) It is well known that DCs such as LCs stimulate proliferation response of T cells specific for an antigen after their presentation of said antigen to T cells, as taught by Sallusto et al (Sallusto et al, p.1109, and figure 4 on page 114), and

3) It is well known in the art that cancer cells shed their antigen. Further, it is well known in the art that encountering with an antigen promotes the maturation and migration of DCs to regional lymph nodes, and presentation of the antigen to naïve T cells by DCs (Sallusto et al, p.1109, and Steinbrink et al, p.1634, first column, submitted by Applicant).

Moreover, contrary to the response assertion, Bigotti's teaching of the **low abundance of LCs in prostate cancer** actually provides motivation for one to make in vitro DCs to administer

into prostate cancer patient. Bigotti et al teach that low-grade carcinomas harbor LCs, which even if not as numerous as, for example, in squamous cell carcinomas of the epidermis, are **nevertherless present, as opposed to the high-grade prostate tumor** (p.81, last paragraph), and that, similar to other cancers, the presence of LCs and HLA class II molecules is correlated with good prognosis in prostate cancer (abstract, p.81). Thus, the low abundance of LCs in prostate cancer would provide motivation for one to use the method of Sallusto et al to make in vitro DCs, capable of activating T cells specific for prostate cancer, to administer into prostate cancer patient, to increase the number of DCs in the patient, because: 1) DCs made by the method of Sallusto et al are the most potent antigen presentation cells, even more efficient than antigen-specific B cells, as taught by Sallusto et al (p.1115, second column, second paragraph), and thus complementary to the anti-cancer action of macrophages, and 2) Similar to other cancers, the presence of LCs and HLA class II molecules is correlated with good prognosis in prostate cancer, as taught by Bigotti et al.

The response further asserts as follows:

Bigotti et al. provides no information control group to compare the number of LCs in the low grade tumor samples with normal prostatetissue. The Examiner has not addressed this issue. To further support this point Applicants provide herewith a copy of an abstract of Troy et al., J. Urol. 160:214-219, 1998, wherein the number of Langerhans cells and the number of dendritic cells were compared between prostatic cancer tissue and adjacent normal prostate tissue. The authors that the number of dendritic cells and Langerhans cells in the normal tissue were greater than in the normal prostatic tissue. They conclude that "there is no active recruitment of DC into

prostate cancer and those DC present are only minimally activate. Further, Applicants provide herewith a copy of Sharma et al., Cancer Res. 59:2271-2276, 1999 which provides that Dunning R-3327 rat prostatic adenoearcinomas cells, a widely accepted model for in vivo experimental studies of prostate cancer, when implanted into rats secrete IL-10. Sub-clones of the R-3327 cells that were selected for differential properties of tumor formation and metastasis. Both the metastatic sub-clone and the epithelial-like sub-clone were found to secrete IL-10. As such, Applicants believe that Bigotti et al. does not-suggest to one of skill in the art that any LCs found in a low grade prostate tumor must be present to uptake and present prostate antigen to T cells as suggested by the Examiner. Bigotti et al. merely suggest that the present of LCs can be used to classify prostate tumor.

As to the passages in Steinbrink et al. regarding the possible reverse effects of IL-10 in some tumors, Applicants direct the Examiner to, in particular, paragraph 3, right column, page 1640 where the authors report "[t]hese contrasting results might be due to the different tumor models use, the varying amounts of IL-10 used, and the different forms of IL-10 (virus IL-10 v IL-10) applied. It was demonstrated that the antitumor effect of IL-10 was dose-dependent and that only very high levels of IL-10 were effective in tumor rejection." The authors continue to conclude that in their model, pretreatment of human DC with IL-I0 induces a state of antigen-specific anergy in cytotoxic CD8+ T cells. Applicants believe that Steinbrink et al support the conclusion that IL-10 is an immunosuppressive agent normally found in many tumors. The additional references cited herein demonstrate that prostate tumor secrete IL-10 and that Bigotti et al. would be interpreted as merely demonstrating a means for classifying prostate tumor samples.

As above, the Examiner has not addressed the issue of the presence of an immunosuppressive environment in the tumor. As above, prostate cancer cells, as exemplified by the rat R-2377 cells, secrete IL-I0. Further, prostate tumors were well known to be weakly immunogenic, and as above, the number of dendritic cells and Langerhans cells were know to be less in prostatic tumor than in adjacent normal prostatic tissue. As such, the presence of any soluble tumor antigen in the tissue of Bigotti el al is irrelevant to the rejection made by the Examiner.

The submission of Troy et al and Sharma et al is acknowledged.

The response has been considered but is not found to be persuasive for the following reasons:

The teaching of Troy et al supports the teaching of Bigotti et al. Troy et al teach that , although the number of dendritic cells and Langerhans cells in the normal tissue were greater than in the normal prostatic tissue, there is, nevertheless, a small amount of **activated** LCs in prostate cancer, significantly more than its **virtual absence in non-cancerous prostate tissue** (Troy et al, abstract). It is noted that it is well known in the art activated LCs are LCs that are exposed to, and capture the antigen and has the ability to present the antigen to T cells. Thus, the teaching of Troy et al support the meaning of the teaching of Bigotti et al that LCs found in a low grade prostate tumor must be present to uptake and present prostate antigen to T cells, and are correlated with good prognosis, and especially in view of the teaching in the art that LCs stimulate proliferation response of T cells specific for an antigen after their presentation of said antigen to T cells, as taught by Sallusto et al (Sallusto et al, p.1109, and figure 4 on page 114), and that encountering with an antigen promotes the maturation and migration of DCs to regional

lymph nodes, and presentation of the antigen to naïve T cells by DCs (Sallusto et al, p.1109, and Steinbrink et al, p.1634, first column, submitted by Applicant).

Concerning Sharma et al, there is no indication that the different clones in the Dunning R-3327 rat prostatic adenoearcinoma taught by Sharma et al represent low grade prostate cancer cells in human. It is noted that not all Dunning rat prostate cells express IL-10. IL-10 is expressed in R'-3327-5' ,and R-3327-5'B cells, but not in R-3327-5'A cells. Which of these cells represent the low grade prostate cancer cells in human are not disclosed.

Moreover, although in some tumors, IL-10 suppresses the immune response, however, even if low grade prostate cancer cells secreted IL-10, one cannot predict the effect of IL-10 on the response of the immune response in low grade prostate cancer, in view of the teaching of Steinbrink et al. As taught by Steinbrink et al, submitted by the response, the effect of IL-10 on T cell response in cancers, whether suppression or stimulating the immune response, depends on the types of tumor (p.1640, second column, third and fourth paragraph).

Concerning the issue of B7, it is a limitation not in the claims, and therefore is not further discussed here.

2. Claim 24 remains rejected under 35 USC 103(a) as being obvious over Sallusto et al, in view of Bigotti G et al, and as evidenced by Inaba et al, supra, and further in view of Cohen, PA et al, 1994 (Cancer Research, 54(4): 1055-8) for reasons already of record in paper of 02/15/07.

The response asserts that the combination of Sallusto et al and Bigotti et al does not teach the composition of the claimed invention. The response asserts that the combined references of

Sallusto et al, Bigotti et al, Inaba et al and Cohen et al do not provide incentive to combine the references to use a lysate of prostate cancer.

The response has been considered but is not found to be persuasive for the following reasons:

The combination of Sallusto et al and Bigotti et al suggests the composition of the claimed invention, supra.

It would have been obvious to use as prostate antigen, a lysate of prostate cancer cells from a prostate cancer patient, because prostate cancer cells would have several prostate cancer-specific antigens, and because a tumor lysate successfully primes the dendritic cells for inducing antigen-specific proliferation of antitumor CD4+ T cells, as taught by Cohen et al, and further because using tumor lysate would be more convenient, and does not require the extra step of purification of the antigen.

3. Claim 26 remain rejected under 35 USC 103(a) as being obvious by Sallusto et al, in view of Bigotti et al, and as evidenced by Inaba et al, supra, as applied to claim 23, and further in view of Lutz et al (of record), for reasons already of record in paper of 02/15/07.

The response asserts that the combination of Sallusto et al, Bigotti et al and/or Inaba et al does not teach the composition of the claimed invention. The response asserts that Luz et al do not prove motivation to make the composition of claim 26.

The response has been considered but is not found to be persuasive for the following reasons:

The combination of Sallusto et al, Bigotti et al and Inaba et al suggests the composition of the claimed invention, supra.

It would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to immortalize the dendritic cells taught by Sallusto et al, Bigotti et al, and Inaba et al, using the immortalizing method taught by Luz et al, because immortalizing dendritic cells would enable maintainance of dendritic cells *in vitro* for long periods of time, as taught by Luz et al.

4. Claims 28-29 remain rejected under 35 USC 103 as being obvious by Sallusto et al, Bigotti et al, Inaba et al, and Cohen et al, supra, as applied to claim 23, and further in view of Taylor et al (of record), for reasons already of record in paper of 02/15/07.

The response asserts that the combination of Sallusto et al, Bigotti et al and/or Inaba et al does not teach the composition of the claimed invention. The response asserts that Taylor et al do not address the teachings of Bigotti et al that the immune response is likely induced in prostate cancer by macrophages. The response asserts that as such the cited references do not teach the composition of claims 28-29.

The response has been considered but is not found to be persuasive for the following reasons:

The combination of Sallusto et al, Bigotti et al, and Inaba et al suggests the composition of the claimed invention, supra.

It would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to cryopreserve the dendritic cells taught by Sallusto et al, Bigotti et al,

Stites, and Cohen et al, using the cryopreservation method taught by Taylor et al, to preserve the previously isolated dendritic cells for later use.

5. Claim 30 remains is rejected under 35 USC 103 as being obvious by by Sallusto et al, Bigotti et al, and Inaba et al, supra, as applied to claim 23, and further in view of Taylor et al (of record), as applied to claim 28, and Lutz et al, of record, for reasons already of record in paper of 02/15/07.

The response asserts that the combination of Sallusto et al, Bigotti et al, Inaba et al, and Taylor et al does not teach or suggest the composition of the claimed invention. The response asserts that Luz et al do not cure the deficiency of the primary references.

The response has been considered but is not found to be persuasive for the following reasons:

The combination of Sallusto et al, Bigotti et al, Inaba et al, and Taylor et al suggests the composition of the claimed invention, supra.

It would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to immortalize the cryopreserved dendritic cells taught by Sallusto et al, Bigotti et al, Inaba et al and Taylor et al, using the immortalizing method taught by Luz et al, because immortalizing dendritic cells would allow maintainance of dendritic cells *in vitro* for long periods of time, as taught by Luz et al.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, LARRY HELMS can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
January 05, 2009

/Larry R. Helms/

Supervisory Patent Examiner, Art Unit 1643